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Title:

Outcomes of non-transitioned cases in a sample at ultra-high risk for psychosis

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Objectives

Two thirds of individuals identified as ultra-high risk for psychosis do not develop psychotic disorder over the medium-term. This paper examines their outcome, including persistent attenuated psychotic symptoms, and incident and persistent non-psychotic disorders.

Method

Participants were help-seeking individuals identified as being at ultra-high risk for psychosis between two and 14 years previously (median=5.7). The current sample consists of 226 participants (125 females; 101 males) who completed follow-up assessment and had not developed psychosis. Mean age at follow-up was 25.5 years (*SD*=4.8).

Results

Significant psychopathology was found; 28% reported attenuated psychotic symptoms at follow-up; 68% of participants experienced non-psychotic disorder over the follow-up period; 48% experienced mood disorder, 34% anxiety disorder and 29% a substance use disorder. For a majority, non-psychotic disorder was present at baseline (90%), and was persistent for 57% of them. Over the follow-up period, 26% of the cohort remitted from a disorder, but 37% developed a new disorder. Only 7% did not experience any disorder over follow up.

The incidence of non-psychotic disorder was associated with higher negative symptoms at baseline. Females experienced higher rates of persistent/recurrent disorder. Meeting the brief limited intermittent psychotic symptoms group at intake was associated with lower risk for persistent/recurrent disorder.

Conclusions

Non-transitioned ultra-high risk cases are at significant risk for ongoing attenuated psychotic symptoms, and persistent/recurrent and incident disorders. The ultra-high risk phenotype, while relatively specific to incident psychosis, also captures patients with a range of emerging or chronic psychopathology. Findings have implications for ongoing clinical care.

Introduction

The period of illness preceding the onset of psychotic disorder has received growing attention since the introduction of criteria for identifying youth at ultra-high risk for psychosis (1). These combine state and trait risk factors to identify young people potentially in the prodrome of psychotic illness. A recent meta-analysis (2) indicated that the average rate of transition to psychotic disorder across samples was 36% after three years. Although this reflects a much higher rate of psychosis than in the general population or other clinical samples, two thirds of those identified as at-risk do not develop psychotic disorder in the medium-term.

One possible explanation is that the majority of individuals referred to at-risk services present with transient psychotic experiences and, although they fulfil at-risk criteria, this is not always indicative of impending psychotic illness (3). Subclinical psychotic experiences often occur in the general population, but persist in only a small proportion of those who report them (4), and an even smaller proportion develop a psychotic disorder (5). Rather than indicating psychotic disorder, these experiences may be related to other psychopathology, such as depression and anxiety (6, 7), which are common in at-risk samples (8-12).

Given the common occurrence of non-psychotic disorders in young people meeting at-risk criteria (8-12) and the declining rate of transition to psychotic disorder in recent cohorts (13, 14), it is important to examine the outcomes of those individuals who do not develop psychosis. Results from small samples show high rates of mood disorder at six (15) and 12-month follow-up (16-18). Anxiety disorders are also common (16, 17). In a large at-risk sample, Addington and colleagues (19) showed that, in the group who did not develop psychosis 29% had mood disorder and 38% had anxiety disorder after one year. These rates dropped to 15% and 32% respectively by two year follow-up (19). Substance use disorders were also prevalent, but also reduced after two years. These high rates suggest that young people meeting at-risk criteria who do not develop psychosis continue to experience significant mental health problems.

It is also possible that non-transitioned cases continue to experience attenuated psychotic symptoms and may still meet at-risk criteria. Rates of attenuated psychotic symptoms at one year follow-up vary from 23% to 42% (16, 18, 19). At two years, attenuated symptoms are evident in 35% (20) and 40% (19) of at-risk samples, and 25% (21) and 50% (22) at 3 years. Continued attenuated symptoms could represent an extended prodrome with transition to psychosis yet to occur. Alternatively, young people with attenuated symptoms may not be prodromal, but their ongoing symptoms may be distressing and disabling in their

own right and may be comorbid with threshold or subthreshold mood or anxiety disorder. Although there are now substantial data on persistent attenuated psychotic symptoms, definitions and rates are inconsistent, making it difficult to ascertain true remission rates.

There is also a lack of data on the course of psychopathology for at-risk young people who do not develop psychosis. In the current study we investigated the presence of attenuated psychotic symptoms, the prevalence and course of non-psychotic DSM-IV diagnoses, and predictors of non-psychotic outcomes in those who did not transition to psychotic disorder from a cohort identified as ultra-high risk between two and 14 years previously [the PACE 400 sample (14)]. Based on the previous studies with short- to medium-term follow-up periods (15-19), we expected high rates of non-psychotic psychopathology in this group.

Method

Participants and procedure

PACE is a specialist clinic for young people at ultra-high risk for psychosis, in Melbourne, Australia. The current data was part of a longitudinal study aiming to reassess all research participants at PACE between 1993 and 2006 (*N*=416). Follow-up interviews were completed by 311 participants (74.8%), 85 of whom had developed psychotic disorder [see (14)]. The current sample consists of 226 participants (125 females; 101 males) who completed follow-up assessment but had not transitioned to psychosis. Figure 1 shows the composition of the current sample.

At baseline, participants were aged 15 to 30 years and met ultra-high risk criteria. These are: 1) attenuated psychotic symptoms, 2) brief limited intermittent psychotic symptoms, and/or 3) trait vulnerability for psychotic illness (schizotypal personality disorder or history of psychosis in a first-degree relative) and deterioration in functioning or chronic low functioning [see (14) for full description of determination of ultra-high risk status of this cohort]. Exclusion criteria for entry to PACE are a previous psychotic episode, organic cause for presentation or past anti-psychotic exposure equivalent to a haloperidol dose of >15 mg.

A previously developed tracking system (23) was used to relocate participants. If participants did not consent to face-to-face assessment, they were asked for a telephone interview or written assessment. This study was approved by the local Research and Ethics Committee. All participants provided written informed consent.

Measures

Current assessment (follow-up): Axis I diagnoses at two to 14 year follow-up were assessed using the Structured Clinical Interview for DSM-IV [SCID-I; (24)]. Face-to-face interview was completed for 194 (85.5%), a telephone interview for 29 (12.8%) and in writing for three participants (1.3%). The Comprehensive Assessment of At-Risk Mental States [CAARMS; (25)] was used to assesses the presence of attenuated psychotic symptoms.

Previous assessments performed at initial presentation to PACE (baseline): Baseline psychopathology was measured using the Brief Psychiatric Rating Scale [BPRS; (26)], Scale of Assessment for Negative Symptoms [SANS; (27)], and CAARMS (25). The BPRS psychotic subscale included items: unusual thought content, hallucinations, suspiciousness and conceptual disorganisation. BPRS affective subscale included items: anxiety, depression, guilt, somatic concerns and tension. CAARMS positive subscales were disorders of thought

content, perceptual abnormalities and conceptual disorganisation. General functioning was assessed with the Global Assessment of Functioning (GAF). Diagnoses were assessed using the SCID-I.

Current IQ was measured using the Wechsler Adult Intelligence Scale-Revised [WAIS-R; (28)] or the Wechsler Abbreviate Scale of Intelligence [WASI; (29)]. Eight of the younger participants were assessed using the Wechsler Intelligence Scale for Children [WISC-III; (30)] as an alternative to the WAIS-R at baseline. IQ was estimated using 1) Ward's (31) 7-subtest estimate of verbal, performance and full-scale IQ (*n*=52); 2) Kaufman's 4-subtest (32) estimate of full-scale IQ (*n*=9); or 3) WASI estimate of verbal, performance and full-scale IQ (*n*=123).

Statistical analyses

Data were examined for the frequency of current attenuated psychotic symptoms, non-psychotic DSM-IV disorders during the follow-up period (current or since baseline) and the course of disorders. Three disorder groups were examined: mood, anxiety and substance use disorders, as well as the frequency and course of any disorder. Somatoform and eating disorders occurred rarely and were not included.

The course of disorders was examined for participants who had diagnostic assessment at baseline and follow-up (*n*=203 for mood/anxiety; *n*=192 for substance use). Participants were classed as '*never'* if the disorder was not present at baseline or during follow-up; '*persistent/recurrent*' if disorder was present at baseline and during follow-up; '*remission'* if disorder was present at baseline but absent during follow-up; '*incident*' if disorder was absent at baseline but present during follow-up (see Figure 2).

To investigate candidate predictors of the course of disorders, participants with incident disorder were compared to participants who never had the disorder. Participants with persistent/recurrent disorder were compared to those with remitted disorder. Candidate predictors were intake group, GAF, BPRS psychotic score, BPRS affective score, SANS total, CAARMS disorders of thought content, CAARMS perceptual abnormalities, CAARMS conceptual disorganization, verbal IQ, performance IQ and full-scale IQ. For primary analyses, predictors with a univariate association at p-value <0.1 were entered together into binary logistic regression to identify the strongest predictors. Age at baseline, gender and length of the follow-up period were always included as predictors in binary logistic

regressions. Analysis was conducted for mood, anxiety and substance use disorders separately, and then for any disorder.

Given the large variability in follow-up period, the cohort was divided into three subsamples based on when they were identified as at-risk: long- (1993-2000, *N*=82), medium- (2001-2003, *N*=77) and short-term follow-up periods (2004-2006, *N*=67). Frequencies are presented for the entire cohort and each subsample. Given the volume of data, some analyses are presented in online supplementary data only, as is exploratory analyses of neurocognitive predictors of the course of disorders.

Results

Sample characteristics

More females completed follow-up than males (55.3% female; χ^2=5.12, *p*=0.02). There were no other significant differences between participants who were followed-up and those that were not. The mean age of participants at baseline was 18.6 years (*SD*=3.3) and 25.5 years (*SD*=4.8) at follow-up. Follow-up was conducted between 2.4 and 14.1 years after baseline (*M*=6.9; *SD*=3.1; median=5.72). Eighty- two (36.3%) participants received trial treatment while attending PACE [cognitive-behaviour therapy (*n*=25); cognitive-behaviour therapy and low-dose antipsychotics (*n*=38); low-dose lithium (*n*=19), all ≤12 months]. There were no significant differences between participants who received trial treatment and those who did not on rates of disorders during follow-up. Further characteristics for each subsample are presented in Supplementary Table 1.

Frequency and comorbidity of non-psychotic disorders at follow-up

Diagnostic outcomes at follow-up are presented in Table 1. Of the entire cohort, 68.1% met criteria for at least one disorder during the follow-up period. Mood disorder was present during follow-up for 48.7%, anxiety disorder for 34.5% and substance use disorder for 29.2%. Proportions were not notably different between subsamples.

For the entire cohort, both mood and anxiety disorders were present in 24.3%, mood and substance use disorders in 17.7%, anxiety and substance use disorders in 13.7% and all three disorders in 10.2%. Patterns of comorbidity were similar in the 1993-2000 and 2003-2006 subsamples, but lower in the 2001-2003 group (see Table 1).

Attenuated psychotic symptoms

The proportion of participants reporting attenuated psychotic symptoms at follow-up that were at or above the threshold for ultra-high risk was 28.3% for the entire cohort, 24.4% for the 1993-2000 subsample, 23.4% for the 2001-2003 subsample, and 41.9% for the 2004-2006 subsample (data missing for 30 of the participants with telephone/written assessment at follow-up).

The co-occurrence of attenuated symptoms and non-psychotic disorders at follow-up is presented in Table 2. For the entire cohort, the presence of attenuated psychotic symptoms was significantly associated with a mood disorder (χ^2=7.81, *p*=0.005) and with any non-psychotic disorder over the follow-up period (χ^2=5.91, *p*=0.02), but not with anxiety and

substance use disorders. Results were similar for the 2004-2006 subsample (mood disorders, χ^2=9.14, *p*=0.003; any disorder, χ^2=8.19, *p*=0.004).

Course of non-psychotic disorders

The frequency of baseline disorder, remission, incidence, persistence/recurrence and absence of non-psychotic disorders is shown in Table 3. Below we report results for the entire cohort. Of the participants who had a mood disorder at baseline (64.2%), 53.8% had persistent/recurrent disorder. In those without mood disorder at baseline, 32.8% developed one. Of those with anxiety disorder at baseline (35.8%), 40.7% experienced persistent/recurrent anxiety. Of those without anxiety disorder at baseline, 29.5% developed one. Substance use disorders were present at baseline for 21.9% individuals (of 192 with available baseline substance use diagnoses). Of them, over half (52.4%) showed persistent/ recurrent substance use disorder over follow-up. Of those without substance use disorder at baseline, 22.3% developed a substance use disorder.

In terms of any disorder, 90.1% of the cohort had any non-psychotic disorder at baseline. Over the follow-up period, 26.0% of the entire cohort remitted from a disorder, but 37.5% developed a new disorder. 57.2% of the cohort had a persistent/recurrent non-psychotic disorder. Only 7.3% never experienced any disorder.

For the most part, the course of disorders were not notably different between subsamples, with the exception of the 2004-2006 subsample presenting with lower rates of substance use disorders at baseline. However, the rate of incident substance use disorder in this subsample was comparable to the other groups.

Predictors of the incident disorder and remission

Baseline symptomatology, GAF, IQ and age were poor predictors of the course of disorder. Gender emerged as a significant predictor of specific disorders, although the overall models were not statistically significant. Being female was associated with persistent/recurrent mood disorder, compared to remitted mood disorder (odds ratio=2.07, 95% CI for odds ratio=1.02-4.23, *p*=0.05), and with incident anxiety disorder compared to never having an anxiety disorder (odds ratio=2.66, 95% CI for odds ratio=1.11-6.39, *p*=0.03).

The incidence of any disorder was associated with higher baseline scores on the SANS (odds ratio=1.14, 95% CI for odds ratio=1.01-1.29, *p*=0.03) compared to never having a disorder. The persistence/recurrence of any disorder, as opposed to remission from any disorder, was associated with being female (odds ratio=2.40, 95% CI for odds ratio=1.12-

5.15, p=0.02). Meeting the criteria for brief limited intermittent psychotic symptoms at intake to PACE was associated with a decreased chance of persistent/recurrent disorder (odds ratio=0.19, 95% CI for odds ratio=0.05-0.72, p=0.01). Despite its variability, the length of follow-up did not predict the course of disorder in the entire cohort.

Predictors of the course of disorders for each subsample and exploratory analyses of neurocognitive performance are presented in online supplementary data.

Discussion

In this study, we examined the clinical outcome for individuals who did not transition to psychotic illness in a cohort identified as ultra-high risk for psychosis between two and 14 years earlier. The frequency and course of mood, anxiety and substance use disorders were examined. Approximately a quarter of cases experienced attenuated psychotic symptoms at follow-up assessment. Non-psychotic disorders were often present at baseline, and tended to persist over the follow-up period. Incident non-psychotic disorder was also common, occurring in over one third of the sample. Baseline and demographic variables were not strong predictors of the course of non-psychotic disorders.

Persistent attenuated psychotic symptoms

Twenty-eight per cent of the current sample reported attenuated psychotic symptoms at follow-up assessment. If considered together with the cases in the cohort that developed psychotic disorder (14), half of the young people who met ultra-high risk criteria at PACE showed continued or recurrent positive psychotic symptoms (threshold or subthreshold).

The presence of attenuated psychotic symptoms may reflect that some individuals are still at risk for psychosis. This is possible since transitions occurred up to ten years after identification of risk in this sample (14), [although most transitions occurred within the first two years]. Alternatively, it may indicate attenuated symptoms occurring in the context of non-psychotic disorders, which may resolve with resolution of that disorder (3, 6, 7). This would be consistent with the idea of "incidental" psychotic symptoms (33). The fact that participants with the shortest follow-up period showed the highest rates of attenuated symptoms, and that their attenuated symptoms were associated with non-psychotic disorders, could support either of these possibilities.

Non-psychotic disorders

Mood disorders were the most common diagnosis during follow-up, specifically major depressive disorder. This was followed by high rates of anxiety disorders, cannabis dependence and alcohol abuse. These rates are higher than would be expected in the general population. A detailed comparison of our cohort with Australian general population data (34) is presented in online Supplementary Table 3. Briefly, the rates of non-psychotic disorders in this cohort were higher than the 12-month prevalence of these disorders for a similar age group in the general population, as well as higher than lifetime prevalence of adults of all

ages. Most notably, the prevalence of mood disorder over the follow-up period (two to 14 years) in our cohort was increased by a factor of five compared to 12-month prevalence and a factor of three compared to lifetime prevalence in the general population.

This would be expected of a selected help-seeking sample. Indeed, many non-psychotic disorders were already present at baseline. The important point is that disorders persisted for approximately half of these young people who did not develop psychosis. In addition, for those without a non-psychotic disorder at baseline, the incidence of new disorders was common. In fact, over a third of the sample developed an incident disorder over the follow-up period. Thus the ultra-high risk criteria might also represent a useful system for identifying young people at risk for chronic and emerging non-psychotic disorder, especially since they are already linked with youth mental health services. This highlights the need for further investigation to develop a better understanding of the risk factors associated with non-psychotic disorder in this population.

We explored positive and negative psychotic symptoms, affective symptoms, functioning, IQ, gender and age as predictors of incident or persistent/recurrent non-psychotic disorder. Being female was associated with a higher risk of disorder than being male, consistent with general population data (34). However, no other baseline variables were associated with the course of a specific disorder, which may be due to a lack of statistical power. Interestingly, higher SANS scores at baseline and not meeting brief limited intermittent psychotic symptoms criteria were associated with the incidence and persistence/recurrence of any disorder, respectively. This could demonstrate the specificity of brief limited intermittent psychotic symptoms to psychotic disorder and, on the other hand, the non-specificity of symptoms measured on the SANS. It may be that some depressive symptoms were interpreted as negative symptoms and rated on the SANS. Alternatively, those with high negative symptoms and depressive disorder may continue to be in the prodrome of a psychotic disorder, as depression and negative symptoms are known to occur during this phase in schizophrenia (35, 36).

Although highly variable, the length of the follow-up period was not strongly associated with the course of disorders. Notably, in the subsample with the shortest follow-up period (2004-2006), persistence/recurrence of any disorder was associated with a shorter follow-up period. This is consistent with the decrease in the rate of non-psychotic disorders that was noted by Addington and colleagues (19). Together with the finding of considerably higher attenuated psychotic symptoms in the 2004-2006 subsample, our data suggest that the time for which participants are monitored may be important over the short-term (first two to

four years), but becomes less important over the longer-term. This has implications for many studies, which typically track at-risk participants for one to three years.

The lack of strong predictors of non-psychotic disorder is distinctly different from the prediction of psychotic illness in at-risk samples, where a number of baseline symptoms are consistently shown to be associated with the onset of psychosis. However, this does not imply that the course of non-psychotic illness cannot be predicted. Rather, it suggests that clinical variables that predict non-psychotic disorder are different from those that predict the onset of psychotic illness, highlighting the need to design studies with a focus on multiple outcomes at inception (37).

The strength of this study is the large sample size recruited from a single site, the long follow-up period and high follow-up rates. The greatest limitation is the variable length of the follow-up period. Although we have presented data for the entire cohort as well as for subsamples of short-, medium- and long-term follow-up, subsamples do differ in some respects and analyses are complicated by this. Moreover, the epochs used are arbitrary.

It is important to acknowledge that we did not document treatment over the follow-up period, which is likely to influence the course of disorder. Another limitation is that follow-up diagnosis of 32 participants was made via telephone or written interview. Finally, females were over-represented at follow-up, which may bias towards higher levels of mood and anxiety disorder.

The current findings demonstrate significant psychopathology in non-transitioned cases two to 14 years after identification of risk. Persistent or recurrent non-psychotic disorders were frequent even though these young people had previously been involved with youth mental health services, albeit in a time-limited manner. Clinically, the results suggest the need for at-risk clinics to include non-psychotic outcomes in their treatment and follow-up plans to provide longer-term care.

We have previously proposed a clinical staging model that posits that severe mental disorders such as schizophrenia, bipolar disorder and severe unipolar depression develop from initial non-specific symptoms, such as depressed mood, anxiety and distress (38). Acquisition of new symptoms, including psychotic symptoms and worsening of emotional dysregulation occurs in some people, who might then meet the at-risk for psychosis criteria. From this clinical picture, a number of trajectories and outcomes are possible, including the major mental disorders noted above, remission, or persistence of subthreshold syndromes. The ultra-high risk criteria were developed to detect incident psychotic disorders and have proved valid to that end. It is not surprising therefore that they identify high rates of

schizophrenia (39). Future studies need to investigate the risk factors for chronic and incident non-psychotic disorder by incorporating variables of interest to non-psychotic outcome in their designs, for example Axis II disorders, mood disturbance, cognitive biases or family history of non-psychotic disorders. This will increase the understanding of the factors associated with the course of disorders in this population, and how they can best be treated.

Text for Figures

Figure 1. Composition of the PACE ultra-high risk cohort and current sample

Note. The current sample (N=226) is indicated in bold. Of the 203 with diagnostic information at baseline and follow-up, 11 were missing substance use diagnoses at baseline.

Figure 2. Definitions used for the course of non-psychotic disorders in this study

Table 1. Rates of Axis I diagnoses during the follow-up period

	Entire cohort N=226		**1993-2000** N=82		**2001-2003** N=77		**2003-2006** N=67	
	N	%	*N*	%	*N*	%	*N*	%
Any disorder	154	68.1	56	68.3	53	68.8	45	67.2
Any mood disorder	110	48.7	41	50.0	34	44.2	35	52.2
Major depressive disorder	92	40.7	35	42.7	29	37.7	28	41.8
Dysthymic disorder	8	3.5	2	2.4	0	0.0	6	9.0
Bipolar I disorder	6	2.7	2	2.4	3	3.9	1	1.5
Bipolar II disorder	3	1.3			3	3.9	0	0.0
Other mood disorders*	2	0.9	1	1.2	1	1.3	0	0.0
Any anxiety disorder	78	34.5	30	36.6	23	29.9	25	37.3
Panic disorder with agoraphobia	11	4.9	2	2.4	3	3.9	6	9.0
Panic disorder without agoraphobia	16	7.1	6	7.3	4	5.2	6	9.0
Agoraphobia without panic	6	2.7	3	3.7	3	3.9	0	0.0
Social phobia	25	11.1	11	13.4	6	7.8	8	11.9
Specific phobia	8	3.5	2	2.4	3	3.9	3	4.5
Generalised anxiety disorder	14	6.2	6	7.3	2	2.6	6	9.0
Obsessive compulsive disorder	7	3.1	3	3.7	2	2.6	2	3.0
Post-traumatic stress disorder	10	4.4	6	7.3	2	2.6	2	3.0
Other anxiety disorder*	6	2.7	2	2.4	2	2.6	2	3.0
Any substance use disorder	66	29.2	27	32.9	21	27.3	18	26.9
Alcohol abuse	23	10.5	10	12.2	8	10.4	5	7.5
Alcohol dependence	20	8.8	10	12.2	5	6.5	5	7.5
Cannabis abuse	7	3.1	2	2.4	3	3.9	2	3.0
Cannabis dependence	33	14.6	16	19.5	9	11.7	8	11.9
Amphetamine/stimulant abuse	15	6.6	6	7.3	5	6.5	4	6.0
Amphetamine/stimulant dependence	10	4.4	3	3.7	4	5.2	3	4.5
Other drug abuse*	14	6.2	4	4.9	6	7.8	4	6.0
Other drug dependence*	7	3.1	3	3.7	1	1.3	3	4.5
Any somatic disorder ǂ	6	2.7	4	4.9	1	1.3	1	1.5
Any eating disorder ǂ	11	4.9	2	2.4	3	3.9	6	9.0
Mood + Anxiety	55	24.3	24	29.3	11	14.3	20	29.9
Mood + Substance use	40	17.7	17	20.7	10	13.0	13	19.4
Anxiety + Substance use	31	13.7	14	17.1	9	11.7	8	11.9
All three disorders	23	10.2	12	14.6	4	5.2	7	10.4

Note: Bipolar disorder refers to non-psychotic cases only.
*Other mood disorders refers to depressive disorder not otherwise specified, bipolar disorder not otherwise specified and substance-induced mood disorders. Other anxiety disorder refers to anxiety disorder not otherwise specified or substance-induced anxiety disorder. Other drug abuse and dependence refers to sedatives, opioids, paint sniffing or hallucinogens.

ǂ Any somatoform disorder refers to body dysmorphic disorder, hypochondriasis, undifferentiated somatoform disorder, pain disorder or somatoform disorder not otherwise specified. Any eating disorder refers to anorexia nervosa, bulimia nervosa, binge eating disorder or eating disorder not otherwise specified.

Table 2. Co-occurrence of attenuated psychotic symptoms and non-psychotic disorders at follow-up assessment

	Entire cohort				**1993-2000**				**2001-2003**				**2004-2006**			
	Attenuated psychotic symptoms (n=64)		No attenuated psychotic symptoms (n=132)		Attenuated psychotic symptoms (n=20)		No attenuated psychotic symptoms (n=50)		Attenuated psychotic symptoms (n=18)		No attenuated psychotic symptoms (n=46)		Attenuated psychotic symptoms (n=26)		No attenuated psychotic symptoms (n=36)	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Mood disorder	42	65.6	57	43.2	13	65.0	24	48.0	8	44.4	19	41.3	21	80.8	14	38.9
Anxiety disorder	31	48.4	46	34.8	12	60.0	18	36.0	6	33.3	17	37.0	13	50.0	11	30.6
Substance use disorder	27	42.2	39	29.5	8	40.0	19	38.0	9	50.0	12	26.1	10	38.5	8	22.2
Any non-psychotic disorder	54	84.4	88	66.6	16	80.0	36	72.0	14	77.7	32	69.6	24	92.3	20	55.5

Table 3. Course of non-psychotic disorders

	Entire cohort (N=203)*		**1993-2000** (N=61)*		**2001-2003** (N=77)		**2004-2006** (N=65)	
PRESENT AT BASELINE			*N*	*%*	*N*	*%*	*N*	*%*
Any disorder	173	90.1	47	94.0	73	94.8	53	81.5
Any mood disorder	145	71.4	33	54.1	61	79.2	51	78.5
Any anxiety disorder	81	39.9	21	34.4	34	44.2	26	40.0
Any substance use disorder	42	21.9	17	34.0	21	27.3	4	6.1
REMISSION								
Any disorder	50	26.0	12	24.0	22	28.6	16	24.6
Any mood disorder	67	33.0	13	21.3	31	40.3	23	35.4
Any anxiety disorder	48	23.6	13	21.3	22	28.6	13	20.0
Any substance use disorder	20	10.4	7	14.0	12	15.6	1	1.5
INCIDENT								
Any disorder	72	37.5	24	48.0	24	31.2	24	36.9
Any mood disorder	19	9.3	9	14.8	4	5.2	6	9.2
Any anxiety disorder	36	17.7	13	21.3	11	14.3	12	18.5
Any substance use disorder	33	17.2	7	14.0	12	15.6	14	21.5
PERSISTENCE/ RECURRENCE								
Any disorder	99	51.6	29	58.0	40	51.9	30	46.1
Any mood disorder	78	38.4	20	32.8	30	39.0	28	43.1
Any anxiety disorder	33	16.2	8	13.1	12	15.6	13	20.0
Any substance use disorder	22	11.5	10	20.0	9	11.7	3	4.6
NEVER								
Any disorder	14	7.3	5	10.0	3	3.9	6	9.2
Any mood disorder	39	19.2	19	31.1	12	15.6	8	12.3
Any anxiety disorder	86	42.3	27	44.3	32	41.6	27	41.5
Any substance use disorder	117	60.9	26	52.0	44	57.1	47	72.3

*11 participants in the 1993-2000 subsample had no available substance use disorder data at baseline. Hence, N for the entire cohort is 203 for mood and anxiety disorders, and 192 for substance use disorder or any disorder. N for 1993-2000 is 61 for mood and anxiety disorders, and 50 substance use disorder or any disorder.

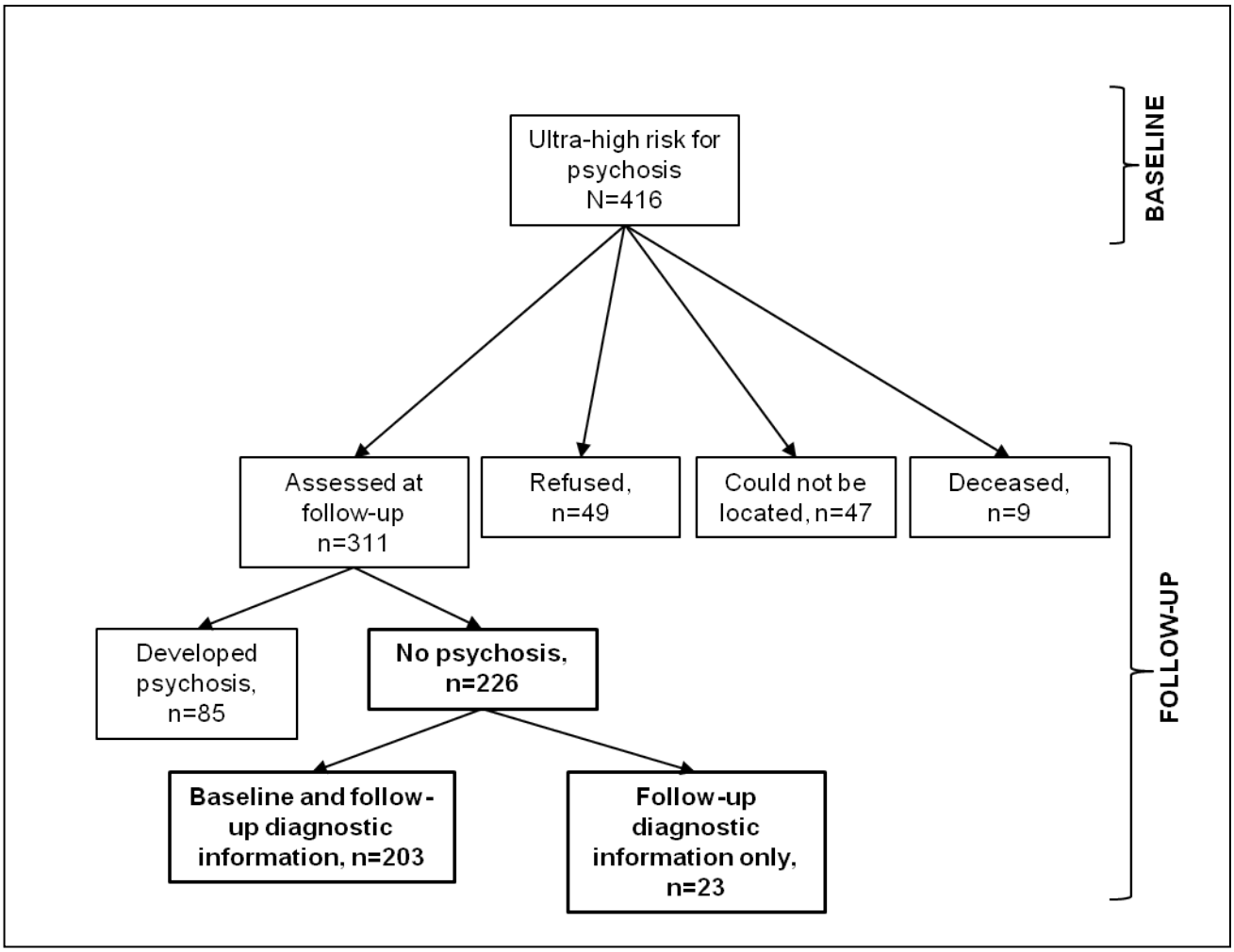

Figure 1. Composition of the PACE ultra-high risk cohort and current sample

Note. The current sample (N=226) is indicated in bold. Of the 203 with diagnostic information at baseline and follow-up, 11 were missing substance use diagnoses at baseline.

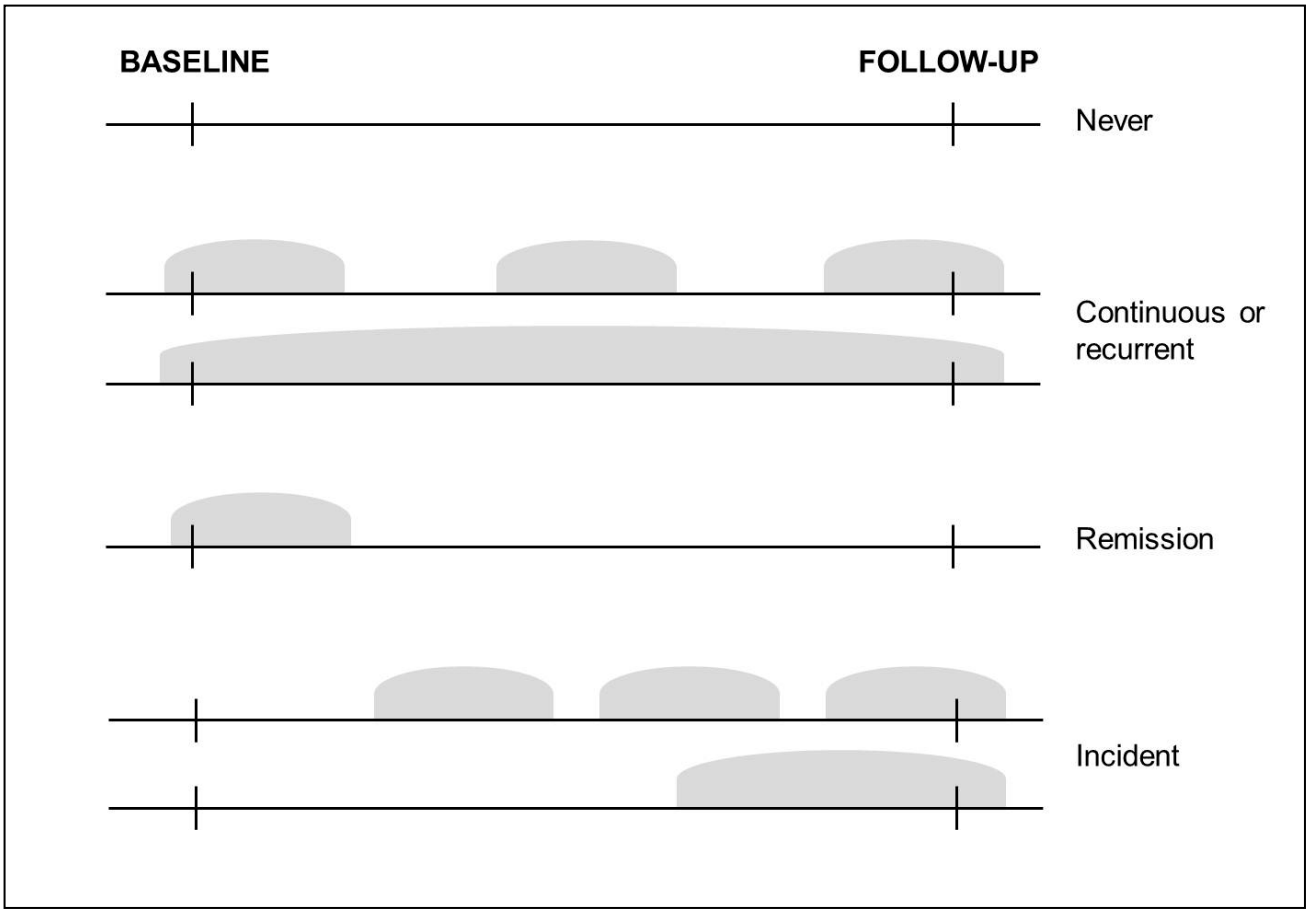

Figure 2. Definitions used for the course of non-psychotic disorders in this study

References

1. Yung A, McGorry PD, McFarlane CA, Jackson H, Patton GC, Rakkar A. Monitoring and care of young people at incipient risk of psychosis. Schizophrenia Bulletin. 1996;22(2):283-303.
2. Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt SJ, Kempton M, Valmaggia L, Barale F, Caverzasi E, McGuire P. Predicting psychosis: meta-analysis of evidence of transition outcomes in individuals at high clinical risk. Archives of General Psychiatry. 2012;69:220-9.
3. Nelson B, Yung A. Psychotic-like experiences as overdetermined phenomena: when do they increase the risk for psychotic disorder? Schizophrenia Research. 2009;108:303-4.
4. Lin A, Wigman J, Nelson B, Vollebergh W, van Os J, Baksheev G, Ryan J, Raaijmakers Q, Thompson A, Yung A. The relationship between coping and subclinical psychotic experiences in adolescents from the general population–a longitudinal study. Psychological Medicine. 2011;1(1):1-12.
5. van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. Psychological Medicine. 2009;39(02):179-95.
6. Wigman J, Lin A, Vollebergh W, van Os J, Raaijmakers Q, Nelson B, et al. Subclinical psychosis and depression: co-occurring phenomena that do not predict each other over time. Schizophrenia Research. 2011;130:277-81.
7. Wigman JTW, van Nierop M, Vollebergh WAM, Lieb R, Beesdo-Baum K, Wittchen HU, Van Os J. Evidence that psychotic symptoms are prevalent in disorders of anxiety and depression, impacting on illness onset, risk, and severity—Implications for diagnosis and ultra–high risk research. Schizophrenia Bulletin. 2012;38(2):247-57.
8. Salokangas RKR, Ruhrmann S, Graf von Reventlow H, Heinimaa M, Svirskis T, From T, Luutonen S, Juckel G, Linszen D, Dingemans P. Axis I diagnoses and transition to psychosis in clinical high-risk patients EPOS project: prospective follow-up of 245 clinical high-risk outpatients in four countries. Schizophrenia Research 138:192-197.
9. Woods SW, Addington J, Cadenhead KS, Cannon TD, Cornblatt BA, Heinssen R, Perkins DO, Seidman LJ, Tsuang MT, Walker EF. Validity of the prodromal risk syndrome for first psychosis: findings from the North American Prodrome Longitudinal Study. Schizophrenia Bulletin. 2009;35(5):894-908.
10. Svirskis T, Korkeila J, Heinimaa M, Huttunen J, Ilonen T, Ristkari T, McGlashan T, Salokangas RKR. Axis-I disorders and vulnerability to psychosis. Schizophrenia Research. 2005;75(2–3):439-46.
11. Velthorst E, Nieman DH, Becker HE, van de Fliert R, Dingemans PM, Klaassen R, de Haan L, van Amelsvoort T, Linszen DH. Baseline differences in clinical symptomatology between ultra high risk subjects with and without a transition to psychosis. Schizophrenia Research. 2009;109(1-3):60-5.
12. Fusar-Poli P, Nelson B, Valmaggia L, Yung AR, McGuire PK. Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: impact on psychopathology and transition to psychosis. Schizophrenia Bulletin. 2014;40(1):120-131.
13. Yung AR, Yuen HP, Berger G, Francey S, Hung TC, Nelson B, Phillips L, McGorry P. Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk? Schizophrenia Bulletin. 2007;33(3):673-81.

14. Nelson B, Yuen HP, Wood SJ, Lin A, Spiliotacopoulos D, Bruxner A, Broussard C, Simmons M, Foley DL, Brewer WJ, Francey SM, Amminger GP, Thompson A, McGorry PD, Yung AR. Long-term follow-up of a group at ultra high risk ("prodromal") for psychosis: the PACE400 Study. JAMA Psychiatry. 2013;70(8):793-802.
15. Lam M, Hung S, Chen E. Transition to psychosis: 6-month follow-up of a Chinese high-risk group in Hong Kong. Australian and New Zealand Journal of Psychiatry. 2006;40(5):414-20.
16. Haroun N, Dunn L, Haroun A, Cadenhead KS. Risk and protection in prodromal schizophrenia: ethical implications for clinical practice and future research. Schizophrenia Bulletin. 2006;32(1):166-78.
17. McGorry P, Yung A, Phillips L, Yuen H, Francey S, Cosgrave E, Germano D, Bravin J, McDonald T, Blair A, Adlard S, Jackson H. Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. Archives of General Psychiatry. 2002;59(10):921-8.
18. Simon AE, Umbricht D. High remission rates from an initial ultra-high risk state for psychosis. Schizophrenia Research. 2010;116(2-3):168-72.
19. Addington J, Cornblatt BA, Cadenhead KS, Cannon TD, McGlashan TH, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, Woods SW, Heinssen R. At Clinical High Risk for Psychosis: Outcome for Nonconverters. The American Journal of Psychiatry. 2011;168(8):800-5.
20. Ziermans TB, Schothorst PF, Sprong M, van Engeland H. Transition and remission in adolescents at ultra-high risk for psychosis. Schizophrenia Research. 2011;126(1-3):58-64.
21. Velthorst E, Nieman D, Klaassen R, Becker H, Dingemans P, Linszen D, De Haan L. Three year course of clinical symptomatology in young people at ultra high risk for transition to psychosis. Acta Psychiatrica Scandinavica. 2011;123(1):36-42.
22. Lemos-Giráldez S, Vallina-Fernández O, Fernández-Iglesias P, Vallejo-Seco G, Fonseca-Pedrero E, Paíno-Piñeiro M, Sierra-Baigrie S, García-Pelayo P, Pedrejón-Molino C, Alonso-Bada S, Gutiérrez-Pérez A, Ortega-Ferrández JA l. Symptomatic and functional outcome in youth at ultra-high risk for psychosis: a longitudinal study. Schizophrenia Research. 2009;115(2-3):121-9.
23. Henry LP, Harris MG, Amminger GP, Yuen HP, Harrigan SM, Lambert M, Conus P, Schwartz O, Prosser A, Farrelly S. Early Psychosis Prevention and Intervention Centre long-term follow-up study of first-episode psychosis: methodology and baseline characteristics. Early Intervention in Psychiatry. 2007;1(1):49-60.
24. First MB, Gibbon M, Spitzer RL, Williams JBW. Structured Clinical Interview for DSM-IV Axis I Disorders. Arlington: American Psychiatric Publishing, Inc; 1997.
25. Yung A, Yuen H, McGorry P, Phillips L, Kelly D, Dell'Olio M, Francey S, Cosgrave E, Killackey E, Stanford C, Godfrey K, Buckby J. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. Australian and New Zealand Journal of Psychiatry. 2005;39:964-71.
26. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychological Reports. 1962;10:799-812.
27. Andreasen N. Scale for the Assessment of Negative Symptoms (SANS). Iowa1982.
28. Wechsler D. Wechsler Adult Intelligence Scale-revised. San Antonio: Psychological Corporation; 1981.
29. Wechsler D. Wechsler Abbreviated Scale of Intelligence. San Antonio: Psychological Corporation; 1999.

30. Wechsler D. The Wechsler Intelligence Scale for Children-3rd ed. San Antonio: Psychological Corporation; 1991.
31. Ward LC. Prediction of verbal, performance and full-scale IQs from seven subtests of the WAIS-R. Journal of Clinical Psychology. 1990;46:436-40.
32. Kaufman AS, Ishikuma T, Kaufman-Packer JL. Amazingly short forms of the WAIS-R. Journal of Psychoeducational Assessment. 1991;9(1):4-15.
33. Yung AR, Nelson B, Baker K, Buckby JA, Baksheev G, Cosgrave EM. Psychotic-like experiences in a community sample of adolescents: implications for the continuum model of psychosis and prediction of schizophrenia. Australian and New Zealand Journal of Psychiatry. 2009 43(118-128).
34. Australian Bureau of Statistics. National Survey of Mental Health and Wellbeing. Canberra; 2007.
35. Yung A, McGorry PD. The prodromal phase of first-episode psychosis: past and current conceptualizations. Schizophrenia Bulletin. 1996;22(2):353-70.
36. Häfner H, Maurer K, Trendler G, an der Heiden W, Schmidt M. The early course of schizophrenia and depression. European Archives of Psychiatry and Clinical Neuroscience. 2005;255(3):167-73.
37. Fowler DG, Hodgekins J, Arena K, Turner R, Lower R, Wheeler K, Corlett E, Reilly T, Wilson J. Early detection and psychosocial intervention for young people who are at risk of developing long term socially disabling severe mental illness: should we give equal priority to functional recovery and complex emotional dysfunction as to psychotic symptoms. Clinical Neuropsychiatry. 2010;7(2):63-71.
38. McGorry PD, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. Australian and New Zealand Journal of Psychiatry. 2006;40(8):616-22.
39. Fusar-Poli P, Bechdolf A, Taylor M, Bonoldi I, Carpenter W, Yung A, McGuire P. At risk for schizophrenic or affective psychosis? A meta-analysis of DSM/ICD diagnostic outcomes in individuals at high clinical risk. Schizophrenia Bulletin. 2013;39(4):923-932.